Codon bias confers stability to human mRNAs(Abstract_要旨)

AUTHOR(S):

Hia, Fabian

CITATION:

Hia, Fabian. Codon bias confers stability to human mRNAs. 京都大学, 2020, 博士(医学)

ISSUE DATE:

2020-03-23

URL:

https://doi.org/10.14989/doctor.k22356

京都大学	博士（　医　学　）	氏　名	ＨＩＡ　ＦＡＢＩＡＮ
論文題目	Codon bias confers stability to human mRNAs （コドンバイアスがヒトｍＲＮＡを安定化する）		

（論文内容の要旨）

The knowledge of how messenger RNA (mRNA) is controlled at the level of post-transcriptional regulation in human cells is particularly valuable in managing or calibrating protein production. According to the central dogma of molecular biology, genetic information in the form of deoxyribonucleic acid (DNA) is converted to protein via ribonucleic acid (RNA) as an intermediate carrier. DNA is firstly transcribed into RNA which is then translated into proteins. However, the relationship between RNA and protein expression is subjected to several layers of regulation. To date, several mRNA-intrinsic properties, such as the 5' or 3' untranslated regions (UTR), have been shown to affect mRNA stability. Despite this, protein abundances cannot be fully explained by mRNA quantity, suggesting that other factors may be involved. However, these other possible mRNA intrinsic factors have not been fully elucidated.

Codons bias is a crucial mRNA-intrinsic feature that affects mRNA stability and translation efficiency in humans and certain model organisms. In this study, this bias refers to differences in the frequency of occurrence of synonymous codons in protein coding genes, hinting at a code beneath a code. Presently, the molecular mechanisms behind this code remain unclear.

In this study, global analysis of codon frequencies of protein coding sequences showed that codons can be clustered into two distinct groups – codons with G or C at the third base position (GC3) and codons with either A or T at the third base position (AT3); the former stabilizing while the latter destabilizing mRNA. Quantification of this codon bias showed that increased GC3 content entails proportionately higher GC content. With this a method was formulated to quantify the optimality of an mRNA based on its GC3-content. Separately, ribosome profiling analysis revealed that ribosome occupancy was correlated with codon optimality to a certain extent. Through the use of codon optimized reporter constructs, RNA stability assays showed that codon optimized mRNAs with high frequencies of GC3 codons were more stable than their AT3-rich, non-optimized counterparts. Additionally, the former were translated more efficiently compared to the latter. As such, the former codons were indicated as 'optimal' and the latter as 'non-optimal' codons.

By the use of frameshifted constructs, the effects of codon bias could be decoupled to reveal two possible modes of mRNA regulation, GC3- and GC-content dependent. Employing an immunoprecipitation-based strategy, heterodimeric proteins ILF2 and ILF3 were identified to be able to differentially regulate global mRNA abundances based on codon bias. These results demonstrate that codon bias is a two-pronged system that governs mRNA abundance.

In summary, a codon optimality-based, translational-dependent pathway of mRNA regulation exists in humans. At present, the factors and mechanisms responsible have not been elucidated. As many biological processes such as cell-mediated immunity and cellular homeostasis and differentiation depend on the intricate regulation of mRNA and proteins, a dysregulation in post-transcriptional and translational processes results in diseases. Harnessing this knowledge potentially allows one to devise strategies for therapeutic intervention of diseases.

（論文審査の結果の要旨）

セントラルドグマにおいて、mRNA の安定性やタンパク質翻訳は、5 'または 3'非翻訳領域（UTR）を始めとした mRNA 上の特徴を通じて制御を受けていることが知られている。加えて、酵母を用いた研究から、同義コドン使用頻度の偏り（コドンバイアス）が mRNA の安定性と翻訳効率に影響を与えることが報告されたが、ヒトにおいてコドンバイアスが mRNA 安定性に影響を及ぼすのかは明らかではなかった。

本研究では、ヒトタンパク質コード配列のコドン頻度の分析により、コドンを 3 番目の塩基に G または C を持つもの（GC3）と A または T を持つもの（AT3）という 2 つの異なるグループにクラスター化できることを見出した。GC3 コドンは mRNA を安定化するが、AT3 は mRNA の不安定化と相関した。GC3 含有量に基づいて mRNA の最適性を定量化する方法を開発し、mRNA 上のリボソーム占有率が、ある程度コドン最適性と相関していることを明らかにした。実験的に、GC3 コドンの頻度が高いコドンを最適化した mRNA は、AT3 リッチの非最適 mRNA よりも安定であり、より効率的に翻訳された。また、RNA 結合蛋白質である ILF2 と ILF3 が、コドンバイアスに応じて mRNA の安定性を制御する分子の一部として機能することを同定した。。

以上の研究は、コドンバイアスを通じた新たなヒト mRNA 制御機構の解明に貢献し、タンパク質産生制御法の開発に寄与するところが多い。

したがって、本論文は博士（　医学　）の学位論文として価値あるものと認める。

なお、本学位授与申請者は、令和２年１月２２日実施の論文内容とそれに関連した試問を受け、合格と認められたものである。

要旨公開可能日：　　年　　月　　日　以降